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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/759,315 | BLECK ET AL. | |
| | Examiner | Art Unit | |
| | ILEANA POPA | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-10,12,14-18,20-26,28 and 30-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12,14-18,20-26,28 and 30-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/28/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/17/2009 has been entered.

Claims 11, 13, 19, 27, 29, and 42 have been cancelled.

Claims 1-10, 12, 14-18, 20-26, 28, and 30-41 are pending and under examination.

***Double Patenting***

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an

invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1-10, 12, 14-18, 20-26, 28, and 30-41 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 36-74 and 94-102 of copending Application No. 11/928,464, in view of Schroder et al. (Biotech. Bioeng., 1997, 53: 547-559, of record).

This is a provisional obviousness-type double patenting rejection.

The instant claims are drawn to a method for transducing host cells by providing an immortal host cell and a plurality of retroviral vectors encoding a gene of interest, contacting the host cell at a multiplicity of infection from about 10 to 1000, repeating the above steps a plurality of time, clonally selecting the host cell expressing the gene of interest, and purifying the protein of interest (claims 1-10, 25, 28, 30, and 31). The retroviral vector is pseudotyped and comprises MoMLV elements, an exogenous promoter, a signal sequence, and an amplifiable marker such as DHFR (claims 12, 14-18, 20, 35, and 36) and the vector encodes at least two proteins, such as immunoglobulin heavy and light chains, arranged in a polycistronic sequence (i.e., the retroviral vector comprises IRES) (claims 22-24 and 39). Clonally selected cells are cultured in the presence of a selection agent such as methotrexate and could express 1, 10, or 50 pg per cell per day of the protein of interest (claims 32-34, 37, and 38), and the host cell comprises from 20 to about 100 integrated retroviral vectors (claim 41).

The host cell can be a CHO or a 293 cell (claim 26) and the host cell can be transduced with at least two different vectors encoding different genes of interest (claim 40).

The application claims recite a method of transfecting a host cell and producing a protein of interest by providing a host cell and retroviral vectors comprising an exogenous promoter, a gene encoding for a protein of interest, contacting the host cell with the retroviral vector at a multiplicity of infection of 1000, and culturing the transduced host cell such that the protein encoded by the gene of interest is produced, wherein between 2 and 1000 copies of retroviral vector integrate into the host cell genome; the host cell could be clonally selected and the protein of interest is further isolated (claims 36-43, 49, 51, 54, 56, 58-67, 69, 71-74, and 94-101). The retroviral vector is pseudotyped and comprises MoMLV elements, a signal sequence, an RNA stabilizing element IRES, at least two gene of interest such as the immunoglobulin genes arranged in a polycistronic sequence, the host cell is a CHO cell (i.e., immortal cell), the host cell secretes 1, 10, or 50 pg per cell per day of the protein of interest, and the host cell could comprise a second retroviral vector encoding a second protein of interest (claims 36-38, claims 44-48, 50, 52, 53, 55, 57, 68, 70, and 102). The application claims do not recite DHFR and methotrexate. Schroder et al. teach the amplification of hATIII expression in CHO cells via DHFR-mediated gene amplification in the presence of methotrexate (Abstract, Introduction, Table I). It would have been obvious to one of skill in the art, at the time the invention was made, to include an amplifiable marker, such as DHFR, into the instant vector and select with methotrexate for increased protein production, with a reasonable expectation of success. One of skill

in the art would have been motivated to do so because Schroder et al. teach that increase synthesis of recombinant proteins in animal cells is commonly achieved by using gene amplification. One of skill in the art would have been expected to have a reasonable expectation of success in making and using such a composition because the art teaches that such a composition can be successfully made and used.

Thus, at the time of the invention, one of skill in the art would have considered the instantly pending claims an obvious variation of the application claims when viewed in light of the teachings of Schroder et al.

The applicant submits that he will file a terminal disclaimer when the other issues are resolved. The applicant's comments are acknowledged, however the rejection will be maintained until a Terminal Disclaimer is filed or claims are amended to obviate the rejection.

***Claim Rejections - 35 USC § 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-10, 12, 14-18, 20, 21, 28, 30-34, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. (Proc. Natl. Acad. Sci. USA,1996, 93: 10371-10376, of record), in view of each Burns et al. (Proc. Natl. Acad. Sci. USA, 1993,

90: 8033-8037, of record), Felts et al. (Strategies,1999, 12: 74-77, of record), Schott et al. (Somatic Cells and molecular Genetics, 1996, 22: 291-309, of record), and Persons et al. (Blood Cells, Molecules, and Diseases, 1998, 24: 167-182, of record).

Mathor et al. teach a retroviral vector encoding human interleukin 6 (hIL-6), wherein the retroviral vector contains MoMLV LTRs, wherein the vector is used to transduce keratinocytes at a MOI of 30, wherein the keratinocytes integrate multiple proviral copies in their genome, and wherein the transduced keratinocytes secrete hIL-6 at a rate of approximately 800 ng per $10^6$ cells per day during their lifetime ( i.e., the cells secrete more than 1 pg per cell per day); the transduced cells are grown as mass cultures or are cloned by limiting dilution (claims 1, 18, 20, 28, 31, 32) (Abstract, p. 10371, column 2, second paragraph, Material and Methods, p. 10372, columns 1 and 2, p. 10373, column 2). Since hIL-6 is secreted, the retroviral vector must necessarily comprise a segment encoding a secretion signal sequence operably linked to the gene encoding for hIL-6 (claim 21). Mathor et al. teach clonal analysis by Southern blot and by radioimmunoassay, wherein the radioimmunoassay is performed on isolated hIL-6 (claims 1 and 30) (p. 10372, columns 1 and 2, p. 10374, p. 13075, column 1 and Fig. 4, p. 10636, column 1). Mathor et al. teach 11 clones with 1 to 15 proviral integrations, i.e., Mathor et al. teach clonally selecting at least 1 or 10 colonies (claims 35 and 36) (p. 10373, Table 1). Mathor et al. also teach that the retroviral vector is produced from packaging cell lines transfected with an envelope plasmid and a vector plasmid, wherein the packaging cell line expresses gag and pol proteins (claims 12 and 14) (p. 10371, column 2 bridging p. 10372).

Mathor et al. do not teach immortal cells (claim 1), nor do they teach 293-GP cells (claim 15), or VSV-G protein (claims 16 and 17). Burns et al. teach producing retroviral vectors pseudotyped with VSV-G, wherein the vectors are produced in 293-G cells and wherein the pseudotyped retroviral vectors are able to mediate stable gene transfer in cell lines such as the BHK cell line (i.e., immortal cells) (Abstract, p. 8033, columns 1 and 2, p. 8035, column 1, second paragraph). Based on these teachings, one of skill in the art would have known that immortal cells could also be used in the method of Mathor et al. and would be motivated to modify the method of Mathor et al. by substituting their secondary cells with immortal cells to achieve the predictable result of obtaining consistent production of desired proteins for unlimited time. Furthermore, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Mathor et al. by using the pseudotyped retrovirus of Burns et al., with a reasonable expectation of success. The motivation to do so is provided by Burns et al., who teach that such a virus has an expanded host range (Abstract, p. 8033, column 2). One of skill in the art would have been expected to have a reasonable expectation of success in making and using such a composition because the art teaches that such a composition can be successfully made and used.

Mathor et al. and Burns et al. do not specifically teach serial transduction to a obtain cell comprising in its genome from 20 to about 100 integrated vectors (claims 1-10 and 41). However, Mathor et al. do teach that protein expression is directly proportional to the integration events (i.e., copy number) (p. 10376, column 1). Additionally, the prior art as a whole teaches that there is a positive correlation between

the MOI and integration events. For example, Felts et al. teach that the advantage of retroviral vectors is that the copy number of integrated provirus can easily be controlled by varying the multiplicity of infection (MOI) (p. 74). Schott et al. teach serially transducing cells with a retroviral vector carrying an internal promoter driving the expression of a gene of interest, wherein higher MOI result in higher integration events and wherein the expression and stability of the gene of interest directly correlates with the number of integrated retroviral vectors (Abstract, p. 292, column 2, p. 294, column 2, second paragraph, p. 295, column 1, p. 302, column 2, first full paragraph, p. 303, column 2 and Fig. 9, p. 308, column 1). Persons et al. teach that repeatedly transducing cells with retroviral vectors at a MOI of 1,000 results in cells comprising 20 copies of integrated retroviral vector (Abstract, paragraph bridging p. 168 and 169, p. 171, column 2, last paragraph, p. 172, column 2, last paragraph, p. 173, column 2, p. 174, column 2, p. 177, column 2, p. 179, column 1, first full paragraph). Based on these teachings, one of skill in the art would have known that serially transducing cells with high MOI would result in increased proviral integration events. It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Mathor et al. and Burns et al. by serially transducing their cells with high MOIs (such as MOIs of 1,000) to achieve the claimed ranges of integration events, with a reasonable expectation of success. The motivation to do so is provided by Mathor et al., who teach the possibility of specifying the level of transgene expression by controlling the integration events (Abstract, p. 10376, column 1). One of ordinary skill in the art would have been expected to have a reasonable expectation of success in doing

so because the art teaches that the level of retroviral vector integration events can be easily controlled by manipulating the MOI. With respect to the limitation of an internal promoter (claim 1), using such was routine in the prior art, as taught by Schott et al. (p. 292, column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Mathor et al. and Burns et al. by further including an internal promoter in their vector to achieve the predictable result of expressing hIL-6 in their cells. With respect to the limitations of one cell secreting more than 10 or 50 pg protein per day (claims 33 and 34), one of skill in the art would have had known to obtain the desired amounts of synthesized proteins by controlling the number of integration events.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

The applicant traversed the instant rejection on the ground that there is a major flaw in the Examiner's reasoning. The flaw is that just as clones with 15 integrations could have had higher levels of protein expression, such clones could have had lower levels of expression as well. A person of skill in the art would recognize that there is no way to predict, based on Mathor, whether additional clones with 15 (or 20 for that matter) integrated retroviral vectors would have higher levels of expression of a protein of interest than observed in the clones with 8 integrated retroviral vectors. This is confirmed by the fourth Bleck Declaration:

> The data in Table 1 of Mathor, which is limited to a maximum of 15 integrations cannot be extrapolated to a situation where there are 20 integrations. It is impossible to do a

> statistical analysis or curve fit based on the data in Mathor. To provide any other interpretation to the data is not scientifically correct. For example, as shown in Appendix 1, the data could indicate a plateau or upside-down U shaped curve as shown. This is why I have previously said it was not proper to extrapolate the data to cells that have 20 integrations. A person of skill in the art would not do this.

The citations to Liu and Stamps do not cure this problem because neither Liu nor Stamps provide any information that can be used to predict whether a cell line containing 20 integrated retroviral vectors will produce more protein than a cell line with 8 or 15 integrated retroviral vectors. The fact that different clones can produce different amounts of protein has no relevance to whether a person of skill in the art would modify Mathor and make clones with 20 or more integrated retroviral vectors.

In fact, the Fourth Bleck Declaration provides a number of scientific papers that show the prior art was very concerned with gene silencing (methylation) of retroviral vectors. In light of this knowledge in the prior art, one of skill in the art would have interpreted the data in Mathor as consistent with showing that increasing retroviral copy number decreases protein expression once a certain number of integrations is reached. Fourth Bleck Declaration, ¶6. When evaluating claims for obviousness, "the prior art as a whole must be considered. The teachings are to be viewed as they would have been viewed by one of ordinary skill." In re Hedges, 783 F.2d 1038, 1041 (Fed. Cir. 1986). Accordingly, "'[i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.'" Id. (quoting In re Wesslau, 353 F.2d 238, 241 (CCPA 1965)).

The applicant argues that the examiner cannot pick and choose arguments from references such as Liu and Stamps while ignoring the great weight of the prior teaching of the references provided in the Fourth Bleck Declaration and in the applicant's previous responses.

With respect to Zielske, the applicant argues that the examiner attempts to limit the impact of Zielske's statements to a particular vector/promoter/transgene system even though the examiner has cited this paper as demonstrating the broader concept that increasing copy number increases protein expression. Clearly the reference does not teach that Zielske's teaching are consistent with the prior art which establishes that gene silencing was a problem and that protein expression either plateaus or decreases after a certain number of integrations. Fourth Bleck Decl., ¶7. In an attempt to cure this defect, the Examiner relies on Schott et al. to support the fact that "protein expression from retroviral vectors comprising an internal CMV promoter does not reach a plateau when increasing copy number above 4." However, Schott only describes clones with up to 9 integrated retroviral vectors. Based on the teaching of Zielske and Mathor, one of skill in the art would expect protein expression to decline or plateau after this number of integrations was reached. Id., ¶8. Thus, this paper has no relevance to the issue of whether one of skill in the art would have been motivated to make the claimed cell lines with greater than 20 integrated retroviral vectors.

The applicant argues that Persons et al. describe the production of retroviral packaging cells that produce infectious retroviral particles. Fourth Bleck Decl., ¶9. These packaging cells are not used for the production of a protein or interest as claimed

and are not host cells according to the claims and as defined in the specification. As such, Persons et al. does not address protein production or the impact of including multiple copies of a retroviral vector in a cell line for protein production. Id. Thus, Persons et al. does nothing to add to a rational basis for the rejection either alone or when combined with the other references. Packaging cells are used for producing infectious retroviral particles, host cells are used for producing protein.

The applicant argues that as pointed out by Dr. Bleck, many of the references cited by Bestor and those included in Paragraph 4 of his Declaration describe silencing *in vitro*. Fourth Bleck Decl., ¶10. Bestor was concerned with the problem of gene silencing *in vivo* because gene therapy requires *in vivo* expression. However, many of the studies on gene silencing are conducted with *in vitro* models.

The applicant notes that the examiner argues that there is nothing in the MPEP indicating that post-filing art cannot be used to provide evidence of what one of skill in the art would have known before an invention was made and that there is nothing in the MPEP indicating that post-filing art cannot be used to rebut applicant's arguments that the prior art would discourage to skilled artisan. The applicant notes that they are unaware of any section of the MPEP that indicates that post-filing art can be used to rebut arguments that true prior art references teach away from an invention. The applicant submits that Supreme Court in Graham v. Deere state the scope and content of the prior art must be considered in formulating an obviousness rejection. (Emphasis added, see also MPEP Section 2141). The Graham factors do not include considering

post-filing art. Accordingly, post-filing art cannot be used to provide a rational underpinning for an obviousness rejection.

The applicant argues that, when viewed as a whole, the prior art would have led in a direction away from the path taken by the applicant. Dr. Bleck has provided a number of prior art references that demonstrate the prior art was extremely concerned that the use of retroviral vectors, especially multiple copies of retroviral vectors, would lead to gene silencing in a wide variety of cell types. Fourth Bleck Decl., ¶4. This prior art would have led a person of skill in the art in a direction away from the path taken by applicant. In particular, the skilled artisan, considering these papers, would have recognized that while introducing a limited number of retroviral vectors into a cell line could increase expression, once more than 10 vectors are introduced there would be gene silencing leading to a plateau or decrease in protein expression from the vectors. As a result, the person of skill in the art would have not introduced the claimed 20 or more vectors into a host cell for production of a protein of interest.

The applicant's arguments and fourth Declaration are acknowledged; however, they are not found persuasive for the following reasons:

The applicant argues that the fact that different clones can produce different amounts of protein has no relevance to whether a person of skill in the art would modify Mathor and make clones with 20 or more integrated retroviral vectors. This is not found persuasive. On the contrary, such knowledge in the art does have relevance to whether one of skill in the art would make clones with 20 or more integrated retroviral vectors.

The argument that the data in Table 1 of Mathor et al., which is limited to a maximum of 15 integrations cannot be extrapolated to a situation where there are 20 integrations is just an argument not supported by any evidence. Based on the teachings in the prior art (including Liu, Stamps, and Mathor et al.), one of skill in the art would have known that protein production is proportional to the number of integrated copies and that retroviral insertion is random and that expression level is dependent on the insertion sites; therefore, one of skill in the art would not conclude that the data in Table 1 indicates a maximum of 15 integrations. Based on the teachings in the art as a whole, one of skill in the art would have had reasonably expected that clones comprising more than 15 integrations would express higher amounts of protein and would have known to look for several clones having higher integration numbers and select the high producer clones.

The applicant argues that the examiner cannot pick and choose arguments from references such as Liu and Stamps while ignoring the great weight of the prior teaching of the references provided in the Fourth Bleck Declaration and in the applicant's previous responses. In response, it is noted that the provided evidence and the previous responses were considered (i.e., not ignored), however, they were not found persuasive. In fact, the examiner replied to each of the applicant's previous arguments and explained why the arguments were not persuasive.

With respect to Zielske, the arguments are not new and were previously addressed.

The applicant argues that, since Persons et al. describe the production of retroviral packaging cells, Persons et al. does nothing to add to a rational basis for the rejection either alone or when combined with the other references. In response, it is noted that Persons et al. is relevant because the reference teaches that, at the time the invention was made, obtaining 20 integration events was routine.

The applicant argues that many of the references cited by Bestor and those included in Paragraph 4 of the fourth Declaration describe silencing *in vitro* due to methylation. This is not found persuasive for the same reasons as above. Specifically, the prior art teaches that methylation is dependent on the integration site, i.e., consistent with the teachings of Liu, Stamps, and Mathor et al. that expression level is dependent on the insertion sites. Gunzburg et al. (The EMBO Journal, 1984, 3: 1129-1135) teach that retroviral integration is random and take place either in active (i.e., the virus is expressed) or in inactive (i.e., the virus is not expressed) chromatin domains (see p. 1129, paragraph bridging columns 1 and 2, p. 1133, column 2, p. 1134, column 1). Based on these teachings, one of skill in the art would have known that the same number of integrations would result in different expression levels, depending on the insertion site. Furthermore, the prior art teaches that the expression and stability of the gene of interest directly correlates with the number of integrated retroviral vectors (see Schott et al. above). One of skill in the art would have known to look for clones comprising high numbers of integrated retroviral vectors and select the ones capable of producing high amounts of protein.

The applicant argues that the Graham factors do not include considering post-filing art. This argument is not material to the instant rejection because no post-filing art was used to reject the claims.

For the reasons set forth above, the applicant's arguments and Declaration are not found persuasive and the rejection is maintained.

6. Claims 1-10, 12, 14-18, 20, 21, 26, 28, 30-38, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. taken with each Burns et al., Felts et al., Schott et al., and Persons et al., in further view of Schroder et al. (Biotech. Bioeng., 1997, 53: 547-559, of record).

The teachings of Mathor et al., Burns et al., Felts et al., Schott et al., and Persons et al. are applied as above for claims 1-10, 12, 14-18, 20, 21, 28, 30-34, and 41. Mathor et al., Burns et al., Felts et al., Schott et al., and Persons et al. do not teach DHFR and culturing the transduced cells in the presence of methotrexate (claims 35-38), nor do they teach Chinese hamster ovary (CHO) cells (claim 26). Schroder et al. teach the amplification of hATIII expression in CHO cells via DHFR-mediated gene amplification in the presence of methotrexate (Abstract, Introduction, Table I). It would have been obvious to one of skill in the art, at the time the invention was made, to include an amplifiable marker, such as DHFR, into the vector of Mathor et al., Burns et al., Felts et al., Schott et al., and Persons et al. for increasing protein production and to use the modified vector for the transduction of CHO cells, with a reasonable expectation of success. One of skill in the art would have been motivated to do so because

Schroder et al. teach that increase synthesis of recombinant proteins in animal cells is commonly achieved by using gene amplification. One of skill in the art would have been motivated to use CHO cells because they are known to be an excellent model cell line for the production of high levels of proteins of interest. One of skill in the art would have been expected to have a reasonable expectation of success in making and using such a composition because the art teaches that such a composition can be successfully made and used. Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that Schroder et al. do not cure the deficiencies noted above. Applicant's argument is acknowledged, however, the rejection is maintained for the reasons above.

7. Claims 1-10, 12, 14-18, 20-24, 26, 28, 30-34, and 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. taken with each Burns et al., Felts et al., Schott et al., and Persons et al., in further view of both Primus et al. (Cancer Res., 1997, 53: 3355-3361, of record) and Kolb et al. (Hybridoma, 1997, 16: 421-426, Abstract, of record).

The teachings of Mathor et al., Burns et al., Felts et al., Schott et al., and Persons et al. are applied as above for claims 1-10, 12, 14-18, 20, 21, 28, 30-34, and 41. Mathor et al., Burns et al., Felts et al., Schott et al., and Persons et al. do not teach at least two different vectors encoding different genes of interest (claim 40). Primus et al. teach a method of expressing a monoclonal IgG2a antibody into a tumor cell,

wherein the tumor cell is transduced with two different vectors, one encoding the heavy and the other encoding the light chain (claim 40), and wherein the transduced tumor cell produces self-reactive antibodies (Abstract, p. 3355, column 1, p. 3356, column 1, first full paragraph, p. 3360, column 2). It would have been obvious to one of skill in the art, at the time the invention was made, to use the method of Mathor et al., Burns et al., Felts et al., Schott et al., and Persons et al. to express antibodies into a cancer cell, as taught by Primus et al., with a reasonable expectation of success. The motivation to do so is provided by Primus et al., who teach that antibody gene transfer into autologous tumor cells offer a new and alternative application in the use of antibodies for the immune therapy of cancer. One of skill in the art would have been expected to have a reasonable expectation of success in making such a composition because the art teaches that such a composition can be successfully obtained.

Mathor et al., Burns et al., Felts et al., Schott et al., Persons et al., and Primus et al. do not teach the two genes of interest being arranged in a polycistronic sequence, wherein the genes of interest are the immunoglobulin heavy and light chains (claims 22-24 and 39). Kolb et al. teach concurrent synthesis of both heavy and light chains of the monoclonal antibody A1 by using a bicistronic expression cassette comprising an internal ribosomal entry site (IRES) (Abstract). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Mathor et al., Burns et al., Felts et al., Schott et al., Persons et al., and Primus et al. by using the expression cassette of Kolb et al. for the production of monoclonal antibodies of interest, with a reasonable expectation of success. The motivation to do so is provided

by Kolb et al., who teach that their method allows for the rapid isolation of cell clones expressing high levels of recombinant antibody. One of skill in the art would have been expected to have a reasonable expectation of success in making such a composition because the art teaches that such a composition can be successfully obtained.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that neither Primus et al. nor Kolb et al. cure the deficiencies noted above. Applicant's argument is acknowledged, however, the rejection is maintained for the reasons above.

8. Claims 1-10, 12, 14-18, 20, 21, 25, 28, 30-34, and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor et al. taken with each Burns et al., Felts et al., Schott et al., and Persons et al., in further view of Naldini et al. (Science, 1996, 272: 263-267, of record).

The teachings of Mathor et al., Burns et al., Felts et al., Schott et al., and Persons et al. are applied as above for claims 1-10, 12, 14-18, 20, 21, 28, 30-34, and 41. Mathor et al., Burns et al., Felts et al., Schott et al., and Persons et al. do not teach a lentiviral vector (claim 25). Naldini et al. teach lentiviral vector for the stable transduction of non-dividing cells (Abstract, p. 263, column 1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Mathor et al., Burns et al., Felts et al., Schott et al., and Persons et al. by using the lentiviral vector of Naldini et al., with a reasonable expectation of success. The

motivation to do so is provided by Naldini et al., who teach that their vector can be used for the transduction of non-proliferating cells such as hepatocytes, myofibers, hematopoietic stem cells, and neurons. One of skill in the art would have been expected to have a reasonable expectation of success in using such a composition because the art teaches that such a composition can be successfully used.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant argues that Naldini et al. do not cure the deficiencies noted above. Applicant's argument is acknowledged, however, the rejection is maintained for the reasons above.

9. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Ileana Popa/
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